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UNITED STATES DEPARTMENT OF AGRICULTURE
BULLETIN No. 405

Joint Contribution from the Bureau of Plant Industry, WM. A. TAYLOR, Chief, and the Bureau of Animal Industry, A. D. MELVIN, Chief

Washington, D. C. PROFESSIONAL PAPER December 5, 1916

LUPINES AS POISONOUS PLANTS

By

C. D. MARSH and A. B. CLAWSON, Physiologists, Drug-Plant and Poisonous-Plant Investigations, Bureau of Plant Industry, and HADLEIGH MARSH, Veterinary Inspector, Bureau of Animal Industry

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PART I.—INTRODUCTION.

SUMMARY OF KNOWLEDGE OF LUPINES AS POISONOUS PLANTS.

EARLY HISTORY AND LATER STUDIES.

The lupines have been known from very ancient times, and are mentioned by many authors, e. g., Theophrastus, Marcus Portius Cato Censorius, and Pliny. The last-named author (ed. 1856, pp. 49–50, 452–453)[1] treats of the lupine at length, especially with reference to its use as a green manure. Several species have been used as cultivated crops in Europe, more especially for the reclamation of sandy soils. It has been used also as a fodder crop, and the seeds ground

NOTE.—This paper will be of special interest to the stockmen of the West.

[1] Bibliographic citations in parentheses refer to "Literature cited," p. 43.

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into meal have been used both for domestic animals and as food for man. In Germany the land utilized for lupine, according to the latest available statistics, is 346,753.3 hectares; on 200,000 hectares of this amount it is cultivated as a green manure. The poorer people among the Greeks and Romans and the Cynic philosophers made use of lupine meal in bread. The bitter principle was recognized not only as disagreeable, but as injurious, and the seed was especially prepared in order to get rid of this property. Among the Greeks the seeds were cooked until soft, to remove the outer skin, then placed in sacks in shallow places on the seashore to wash out the bitter principle. Afterwards the seeds were dried, ground in a hand mill, and baked into a poor bread. Only the poorest people used this meal unmixed, but others mixed it with other kinds of meal, making a more digestible flour. (Landerer, 1852.) Because the lupines were planted in Maina and there used for food, the people in that region were known as "Lupinophagi." Lupine meal was also used by the ancient Egyptians, and is still used in Andalusia, Corsica, and Piedmont. (Cornevin, 1893, p. 314.) In modern times lupine meal, after a process of "Entbitterung," has been used to some extent as food for animals.

As a medicine, lupine seeds have been used since ancient times. Pliny (ed. 1856, p. 452–453) enumerates 35 different uses. The main uses, however, seem to have been as a cathartic and as a vermifuge. For the latter it was used as an external application as well as internally.

Bellini (1876) reports in detail cases of poisoning in man from using a decoction of lupine as an enema. He states that Averrhoes and Hofman pointed out the poisonous properties of the plants, and that Paullus, 1708, reports a case of poisoning of a boy by an enema. The reference to Averrhoes and Hofman could not be verified, as apparently they only mentioned the plants as a vermifuge. The symptoms mentioned by Bellini are dyspnœa, defective sight, dilated pupils, and stupor. These symptoms, as will be seen later, compare fairly well with those of poisoning by the lupine alkaloids.

Isolated cases of poisoning by lupines were noted as early as 1860, but it was in 1872 and the following years that heavy losses of sheep occurred in northern Germany. While there is evidence that some animals are poisoned by the alkaloids, most of the cases, and practically all of the losses, have been from the use of lupine hay and are caused, as will be seen later, by ictrogen. The occasional poisoning of cattle and horses reported in Europe appears to have been from the use of the seed and is alkaloidal poisoning. Sheep are also poisoned in this way, but the great losses which have stimulated the extensive investigation of the subject have been by ictrogenic poisoning of sheep.

In America the first published report of losses of sheep is by Chesnut (1899, p. 404–405), and this report with the papers of Wilcox (1899), Chesnut and Wilcox (1901, p. 100–110), and Slade (1903), comprise all that has been published up to the present time. Other authors have mentioned the subject, but their material is all taken from the reports of Wilcox, and Chesnut and Wilcox. The first general account of lupine poisoning in America is by Wilcox (1899). A much more extended account is given by Chesnut and Wilcox (1901, p. 100–110), with details of cases and symptoms. Wilcox notes that mature plants are the more poisonous, and Chesnut and Wilcox definitely state that the toxic principle is mainly in the pods and seeds and that lupine hay should be cut after the seeds are shed. Both Wilcox, and Chesnut and Wilcox apparently consider the poisoning of sheep in America as similar to the disease called "lupinosis" in Germany, although Chesnut and Wilcox (1901, p. 109) state that the "chronic form of the disease" has not been recognized in America. Sollmann, in an unpublished report of a laboratory study of American lupines, a report made under the direction of the Bureau of Plant Industry, which will be discussed more fully later, states that he failed to find evidence of the presence of ictrogen and gives details of the symptoms produced by the alkaloidal substances extracted by him. His work was not connected with field investigations, but the results, viewed in the light of present knowledge, clearly indicate the probability that the field cases of poisoning by lupine in America are not cases of "lupinosis" in the sense in which the term is used in Europe, but are the result of alkaloidal poisoning. The field investigations reported in this paper establish without a doubt the fact that, so far as observed, all cases of poisoning of range sheep by lupines must be considered as due to the alkaloids and not to ictrogen. These field investigations are in entire harmony with the preliminary laboratory study by Dr. Sollmann, although carried on in an independent way without reference to the preceding results obtained in the laboratory.

ANIMALS POISONED BY LUPINES.

While the losses of domestic animals have been mainly of sheep, other animals also are poisoned—horses, cattle, goats, swine, and fallow deer—and laboratory experiments on small animals indicate that none are immune to the effects of the toxic substances.

Wilcox (1899) states that in Montana a few horses have been poisoned, and Chesnut and Wilcox (1901 p. 100–110) give specific instances. Poisoning of horses on the range or in pastures is not common, but is known to occur. Dammann (1902) states that cattle are affected by the alkaloid, and cases of the poisoning of cattle on the range have been reported in America, although the cases are not very well authenticated.

LOSSES FROM LUPINES.

The losses from "lupinosis" in Europe have in some years been very great. In 1880, in Pomerania the loss of sheep was 5.89 per cent (Cornevin, 1893, p. 316). It is stated that in some herds in northern Germany the loss was as great as one-half to three-fourths of the total number.

The known losses in America are very heavy. Chesnut and Wilcox (1901, p. 106) tell of one case, among others, in which out of 2,000 sheep trailed over a region covered with a large quantity of lupine 1,000 were sick and 700 died. In another case 1,150 died out of 2,500 (p. 104). Losses of several hundred are not at all uncommon, and occasionally the deaths may be nearly 50 per cent of the whole number. More complete knowledge of the losses has been obtained in Montana than in any other State, because Montana has been under close observation for many years, and it is very possible that this State suffers more than others, but more or less similar conditions are found in other western States in which the mountain regions are used for sheep grazing. It is probable that the lupines rank as a close second to Zygadenus in causing losses of sheep.

DISTRIBUTION OF LUPINES.

While lupines are found in the eastern United States rather sparingly, and are there represented by only three species, in the Western States there is a large number of species, and these frequently grow in large masses, so that sometimes they are cut for hay. They form an important factor in the number of forage plants. Horses seem to be especially fond of them and will sometimes eat the green plants with great greediness.

Of the species of lupines in America, only a few have been used in this investigation. One of these, *Lupinus sericeus*, is illustrated in figure 1. A thorough systematic study of the genus is in progress by the Bureau of Plant Industry, and further work is being prosecuted for future publication, dealing with the characteristics of the different species from the standpoint of chemistry and pharmacology, as well as from the standpoint of field experimentation.

COMMON NAMES OF LUPINES.

The lupines are known under a large number of common names. Among these are sundial, old-maid's bonnets, Quaker's bonnets, Indian beans, wild beans, blue pea, and blue bean. In some sections the name loco is used, but this is generally by those who do not know the true locoes.

ALKALOIDS OF LUPINES.

No investigations of the alkaloids of American lupines have been published, but the European lupines have been the subject of ex-

FIG. 1.—Lupine (*Lupinus sericeus*).

tended study, and the literature, especially of the chemistry of the alkaloids, is very large.

Cassola (1834) attempted to isolate the alkaloid of *Lupinus albus*, but probably did not obtain the pure alkaloid. Landerer (1852)

obtained a substance that showed a beginning of crystallization, which he called lupinin. Beyer (1871), found an alkaloid in lupine from a study of *Lupinus luteus*. Baumert issued a series of papers from 1881 to 1889. Baumert (1886) summarizes the knowledge to date and announces definitely the presence of two alkaloids in *Lupinus luteus*, lupinin ($C_{21}H_{40}N_2O_2$), and lupinidin ($C_8H_{15}N$). Schmidt (1897), Davis (1897), Callsen (1899), Schmidt (1904), and Bergh (1904) summarize and bring the subject to date with extensive additions to the detailed chemistry of the alkaloids. Schmidt (1897) states the alkaloids as lupinin ($C_{21}H_{40}N_2O_2$), lupinin ($C_8H_{15}N$), "dextrorotatory-lupanin" ($C_{15}H_{24}N_2O$), and inactive lupanin ($C_{30}H_{48}N_4O_2$). These are found in the lupines examined, as follows:

Lupinus angustifolius	dextrorotatory-lupanin.
Lupinus albus	dextrorotatory-lupanin. inactive lupanin.
Lupinus luteus	lupinin. lupinidin.
Lupinus niger	lupinin. lupinidin.
Lupinus perennis	dextrorotatory-lupanin.

Lupinidin is identical with spartein $C_{15}H_{26}N_2$ (Muenk, 1914, p. 394).

Callsen (1899) gives an extended account of the chemistry of the alkaloids of *Lupinus angustifolius* and *L. perennis*. Willstätter and Fourneau (1902) give experimental evidence that the formula of lupinin is $C_{10}H_{19}ON$. Schmidt (1904) and Bergh (1904) in extended papers discuss further the alkaloids and state that another alkaloid is found in *Lupinus perennis*, oxylupanin ($C_{15}H_{24}N_2O_2$).

Liebscher (1880), Löwenthal (1888), and Raimondi (1891) give details of the pharmacology of the lupine alkaloids. The action of all is practically the same but differs quantitatively. Liebscher states that lupinidin is 10 times as active as lupinin. There is a direct paralysis of the medulla and cord, the respiratory center being first paralyzed, and then the vasomotor. This is accompanied by weakening of the heart. There is a fall in blood pressure, a slowing of the pulse, and dilation of the pupils. Death is produced by asphyxia, with which are associated convulsions.

There is no curare action. The dose required to produce any symptoms is ordinarily fatal. The alkaloids are less poisonous for mammals than for cold-blooded animals. Small repeated doses produce no effect, nor do they establish a condition of tolerance.

ICTROGEN.

Early in the investigation of the poisoning of domestic animals in northern Europe by lupines, causing the disease which came to be known as "lupinosis," it was observed that these were not cases of poisoning by the recognized alkaloids of the lupines. Lupinosis has

a definite line of symptoms distinctly different from those produced by the alkaloids, especially characteristic being a hepatitis, which produces a jaundice exhibited in the conjunctiva and visible mucous membranes of the living animal. Kühn (1880), Roloff, (1883), Arnold and Lemke (1881), as well as others, found that the intoxication known as lupinosis could not be produced by alcoholic extracts, but was produced by the marc of the seeds; if the poisoning were alkaloidal, the reverse would be the case. Dammann (1902, p. 343) states that the plant often becomes more toxic on keeping. Moreover, while the alkaloids are always present the ingredient producing lupinosis is inconstant. The plants raised on some fields always produce poisoning, while on others they are harmless (Raimondi, 1891). It was found (Dammann, 1902, p. 342) that the substance producing the disease is insoluble in alcohol, ether, glycerine, and fatty oils, and is soluble with difficulty in water. It is not readily destroyed by dry heat, but steam under pressure makes it harmless. This hypothetical substance was called ictrogen by Kühn (1880) and lupinotoxin by Arnold and Schneidemühl (1883). It has only been recognized by its physiological action.

Ictrogen is not considered to be a product of the metabolism of the lupine, but to be the result of the growth of microorganisms upon the plants. This explanation is not based, however, upon any experimental evidence, but is reached by a process of elimination of other possible theories. This is the theory advanced by Dammann (1902, p. 341–343). Other theories of the cause of lupinosis have been advanced. For example, Zürn (1879) propounded a theory that the disease is produced by microorganisms in or on the lupine leaves; in other words, that lupines do not cause the disease, but simply serve as a carrier. This theory has not been taken very seriously by others, while the theory that the disease is produced by ictrogen and that this substance is produced through the action of some unknown microorganisms upon the lupines is quite generally accepted as the most probable explanation.

PART II.—EXPERIMENTAL WORK.

PHARMACOLOGICAL INVESTIGATION BY SOLLMANN.

SCOPE OF THE WORK.

A series of experiments upon Montana lupines, identified as *Lupinus sericeus*, *L. leucophyllus*, and *L. cyaneus*, was conducted by Dr. Torald Sollmann, under the general direction of V. K. Chesnut, then in charge of the work on poisonous plants in the United States Department of Agriculture, and following is a report of the results.

Eighteen animals, rabbits and guinea pigs, were fed upon pods and seeds with no results, none of them eating enough to produce toxic effects.

Extractions were made of the seeds and pods, and impure alkaloids were obtained. The experience in this work leads to the suggestion of the following method of extraction:

Moisten the powdered drug with alcohol containing 1 per cent of HCl; pack in percolator; macerate with alcohol; percolate with alcohol until the percolate gives only small turbidity with Mayer's reagent. Mix the percolate with sand and evaporate the alcohol. Treat the residue repeatedly with warm water, until it gives off only a slight reaction with Mayer's reagent. To the united filtrate add Mayer's reagent to complete precipitation. Wash the precipitate, suspend it in a little water, and decompose with H_2S; filter.

Evaporate the filtrate to a small volume, add an excess of $Ca(OH)_2$, filter, exhaust the precipitate and filtrate separately with ether, as quickly as possible, neglecting the last traces. Evaporate the ether. Treat the residue with absolute alcohol acidulated with H_2SO_4. Let stand 24 hours. The precipitate will contain the lupinidin, the filtrate the other lupine alkaloids. These will require further purification.

CHARACTERS OF THE ALKALOIDS.

Physical characters.—The physical effects of the aklaloids make it likely that they are similar to those occurring in the European species. Several of these characters were observed in the course of the isolation of the alkaloids.

The (impure) alkaloids were obtained as brown oily liquids of a strongly alkaline reaction and a strongly bitter taste. They were easily soluble in water and in alkalies. They were slightly soluble in petroleum ether. No crystals were obtained. During their separation a strong odor resembling conin, characteristic of lupinidin, was perceptible, especially when strong soda was added. The isolated alkaloids were almost odorless, but again developed the odor very strongly when 10 per cent soda was added.

Chemical characters.—Strongly heated, they boiled and evolved dense, white fumes. Strong sulphuric acid, cold or heated, alone or with formaldehyde or bichromate, gave only browning. Strong nitric acid also gave no characteristic reactions.

Precipitation reactions.—The alcoholic solution gave partial precipitation with sulphuric acid. The dilute neutral aqueous solutions of the chlorid or sulphate behaved as follows:

NaOH (1 per cent): Slight precipitate.

NaOH (strong): Precipitate, partly soluble n excess of the soda.

$(NH_4)OH$: No precipitate.

Na_2CO_3: No precipitate.

Mercuric chlorid: Amorphous precipitate, easily soluble in excess of HCl. The precipitate was incomplete, giving further precipitate with Mayer's reagent, and also the lupinidin test with alcoholic sulphuric acid.

Picric acid: Fair amorphous precipitate.

Tannin: Precipitate, soluble in excess.

Iodin in KI: Good amorphous precipitate.

Pot. ferrocyanid: No precipitate.

Pot. bichromate: No precipitate.

Nature of the alkaloids.—The alkaloids were not obtained sufficiently pure to make definite characterizations possible. Their close agreement with those obtained from the European species in physiological action and fatal dose make it very probable that they are closely related, if not identical. Lupinidin was fairly well identified by the conin odor, by the insolubility of the double chlorid formed with mercury, and by the insolubility of the acid sulphate in absolute alcohol. The precipitation by these reagents was not complete, so that there must be other alkaloids present, presumably lupinin and lupanin. This portion of the work needs further elaboration.

The yield of crude alkaloids in the extraction was as follows:

Specimen IV: *Lupinus sericeus*, parasitized pods, 0.02 per cent from alkaline extract; 0.133 per cent from watery extract.

Specimen V: *Lupinus cyaneus*, seed, 2.462 per cent.

Gerhard found from 0.5 to 1.2 per cent in the European lupines.

TOXICITY OF THE EXTRACTS.

The various extracts, prepared as described, were administered to rabbits and guinea pigs, by mouth, stomach tube, and hypodermically. The symptoms were practically identical, and will be described later. It was found:

(*a*) That the toxic principles must be alkaloidal rather than ictrogenic.

(*b*) That the fatal dose of the drug (as extracts) to rabbits by stomach, in the case of the seeds of *Lupinus sericeus* and *L. leucophyllus*, was between 30 and 50 grams per kilogram, with the seeds of *L. cyaneus* between 70 and 100 grams per kilogram, and with empty pods of *L. sericeus* and *L. cyaneus* over 100 grams per kilogram.

(*c*) That the fatal dose of the crude alkaloids (in the purest form in which they were used, from Specimen V) lies, for rabbits, gastric administration, between 1.2 and 2.4 grams per kilogram; for rabbits, hypodermic administration, between 0.123 and 0.246 grams per kilogram (agrees with Löwenthal's (1888) figures for lupinidin and lupanin, viz, 0.2 and 0.4); for guinea pigs, hypodermic administration, between 0.052 and 0.1 gram per kilogram.

(*d*) That the alkaloids are five to ten times as toxic for rabbits when given hypodermically as when given by the stomach tube.

(*e*) That guinea pigs are about twice as susceptible to the poison, when given hypodermically, as rabbits are.

(*f*) That repeated administration of the poison to animals did not increase their susceptibility, as is shown by the fact that rather prolonged feeding was not fatal, and that no tolerance is produced in this manner, as is shown by rabbits 77 and 78 A. The animals in either case, after having been injected repeatedly, died from the last dose, although these doses were not very greatly above the fatal limit.

SYMPTOMS OF LUPINE POISONING.

It will be useful to describe the typical course, which occurs with only minor variations when any of the extracts are administered. The symptoms set in with a general depression. The animal is very quiet, sits flat with ears laid back; the respiration is rapid, labored, and irregular. The temperature is not altered in a constant manner. After a time it is noted that the animal, while apathetic

if left alone, is quite excitable when disturbed. The reflexes are heightened. The movements are brusque and exaggerated. The depression gradually deepens; the animal partly loses control of its hind legs, so that these tend to drag. Often the animal lies on its belly, the head on the floor and legs spread out. It is still able to walk. It soon loses this ability and sits or lies still. When disturbed, it reacts with shivering, and becomes more and more convulsive. Stimulation now produces more or less violent spasms, the first spasm being strongly tetanic. The animal may assume the strychnin position, with legs stretched out, and back arched in; or it may rise on its feet, the back arched upward. The spasm soon becomes clonic and incoordinated, the animal pawing the air in an aimless manner. This is followed by relaxation, and the animal remains quiet unless disturbed, which disturbance would cause another spasm. After a time the convulsions occur spontaneously. In milder cases there may be no general convulsions, but twitching of isolated muscles—of the face, ears, neck, back, and extremities. The head may swing in a rhythmical pendulum movement. The respiration during this convulsive paralytic condition is slow, shallow, and irregular. The pupils are variable, but need not be dilated (which speaks against the view that they are asphyxial; the mucous membranes are also a bright pink). Many animals urinate copiously. The animals may remain on the abdomen or recover a sitting posture for some time after the onset of the convulsions, but after a time they fall on the side. The respiration becomes gasping. Asphyxial convulsions set in, and the respiration stops from half a minute to 1 minute before the heart.

The depressant and convulsive symptoms agree with those described by Löwenthal (1888), Gemma (1882), and Raimondi (1891) for European lupine alkaloids.

It is not possible to make any general statement as to the time required for the development of the different symptoms, since this is extremely variable. It is remarkable, however, that a considerable time may elapse before any pronounced symptoms appear, and this even when the solutions are administered under the skin. It is to be noted that doses which are little below fatal produce only very slight symptoms.

Recovery may occur from any stage and is usually so complete that the animal gains on its original weight. The intoxication leaves no post-mortem lesions, gross or microscopical.

OPERATIVE EXPERIMENTS WITH LUPINE ALKALOIDS.

The effects on blood pressure, respiration, etc., were studied on five dogs, anæsthetized with morphin and ether, and arranged for tracings. The alkaloidal extract of Specimen V (seeds of *Lupinus*

cyaneus) was injected into the femoral vein, in progressively increasing doses. The dose is calculated as grams of drug (not of alkaloid) per kilogram of body weight. Arranged by doses, the effects were briefly as follows:

SMALL DOSES OF 0.1 TO 0.4 GRAM PER KG.

Respiration: First quicker and deeper; then somewhat slowed; irregular, and shallow.
Carotid blood pressure: Rise, fall, rise, normal.
Heart: Rate somewhat quickened; strength somewhat diminished.

TOXIC DOSES OF 0.5 TO 0.75 GRAM PER KG.

Respiration: First quickened and deeper; then somewhat slowed, irregular, and shallow; may stop.
Carotid blood pressure: Rise, then great fall; effect of sciatic stimulation lessened.
Heart: Rate first slowed, then quickened; when vagi were cut, slowed; strength, weakened.

VERY LARGE DOSES OF 0.9 TO 6.25 GRAMS PER KG.

Respiration: For a few moments deeper; then very shallow and stops.
Carotid blood pressure: First slight rise, then great fall.
Heart: Rate first slowed, then quickened, then stopped; strength weakened.
Convulsions may occur from 1 gram up.

DISCUSSION OF EFFECTS.

Respiration.—The respiration shows a short stimulation (increase of rate and depth), followed by depression (slowed, irregular, shallow); with the larger doses it stops before the heart. The action is probably on the centers, for it occurs after section of the vagi, and when stoppage has occurred it can not be revived by asphyxia, slapping, or stimulation of the sciatic, or injection of saline. No recovery occurs from even a just fatal dose after an hour of artificial respiration. The respiratory center is the first vital center to give out completely.

Blood pressure.—This shows a short, moderate rise, followed by a more lasting fall, which is quite marked with the larger doses, even those which are not fatal. Although the changes often coincide with respiratory changes, the two are not interdependent, for they may occur independently, and blood pressure changes occur even during artificial respiration and are not influenced by the latter. Whether the changes were central or peripheral was not investigated directly; but, from the fact that when vasomotor paralysis exists stimulation of the sciatic is sometimes effective and sometimes ineffective when asphyxia is effective, it is rendered very probable that the action is central. The vasomotor paralysis may precede, coincide, or follow that of respiration. It may be partial or so nearly complete that the pressure sinks to some 20 millimeters with a good heart action.

The heart rate.—With toxic doses there is first slowing, then quickening; with minimal and maximal doses, there is usually quickening only. The slowing and secondary quickening occur equally well when the vagi are divided; they are therefore at least partly peripheral. They are not always accompanied by changes in the strength

of the heart, hence they are probably not muscular. Further, when the heart is quickened by large doses, electric stimulation of the vagus has but little effect. The drug may therefore be said first to stimulate and then depress the vagus end mechanism. It may have a similar action on the vagus center.

Strength of the heart.—This is affected only by rather large doses, but it is then always depressed. Experiment 87 shows that the life may be kept up with a complete vasomotor paralysis, if the heart beats well. This tends to show that the stoppage of the heart, which forms the final cause of death, must be due to paralysis of its muscles. This is confirmed by the fact that it can not be revived by injection of normal saline.

Convulsions.—Convulsions were observed in but two of the five cases. This may be due to the anæsthetic or to the difficulty of securing proper dosage. When observed, however, they preceded respiratory distress and were not connected with any change in blood pressure, so that it seems that they are produced by a direct central action.

Skeletal muscle.—The existence of convulsions in the last stages, as well as the result of stimulation of peripheral and of the sciatic, show that muscle and nerve are not paralyzed.

Cause of death.—The following vital functions are eventually paralyzed by the lupine: Respiratory center; vasomotor center; cardiac muscle; the last named being the last to become paralyzed and being the final cause of death.

SUMMARY.

The results of the investigations are in many respects incomplete and emphasize the need of a more exhaustive chemical and pharmacological study of the American lupines. They have shown, however, that these lupines contain alkaloids which are toxic or fatal if a sufficient quantity of the plant is consumed, but which are harmless if the consumption is below a certain limit. Up to this point the lupines may be a useful food if due precautions are observed that the limits are not surpassed. These alkaloids could also be largely removed by leaching with water. The ictrogen, which is especially feared in Europe, was not found in any of the American samples. It would be of great importance to determine whether this ictrogen is uniformly absent, for if it is not, much more stringent precautions would be necessary.

CONCLUSIONS.

1. Feeding with the lupines does not produce any symptoms in rabbits and guinea pigs, as a sufficient quantity is not taken in this manner.

2. The injection of extracts, by stomach or skin, is fatal if sufficiently large doses are used.

3. No ictrogen was found in any of the six specimens.

4. The toxic constituents are alkaloidal and seem to agree with those of the European species.

5. These alkaloids produce a stimulation and then a paralysis of the following structures: The respiratory and vasomotor centers, some convulsive centers, the vagus end mechanism, and perhaps the vagus center. Large doses given intravenously paralyze the heart muscle. The convulsions do not appear to be purely asphyxial.

6. Pronounced symptoms are seen only when almost fatal doses are given; smaller amounts do not produce any conspicuous effects. When death does not occur acutely, there are no late effects. Repeated administration has no influence on the action.

7. The cause of death is paralysis of respiration. Death occurs, with hypodermic administration, in 12 minutes to 2½ hours; when given by stomach, in 10 minutes to 3½ hours. The symptoms set in only shortly before death.

8. The fatal doses for rabbits by the stomach, figured for the original drugs, are as follows: For the seed of *Lupinus sericeus* and *L. leucophyllus*, between 30 and 50 grams per kg.; for the seed of *L. cyaneus*, between 70 and 100 grams per kg.; for the hulls of *L. cyaneus*, and *L. sericeus*, over 100 grams per kg.

9. The fatal dose of the crude alkaloid for rabbits, gastric administration, lies between 1.2 and 2.4 grams per kg.; for rabbits, hypodermic administration, between 0.123 and 0.246 gram per kg.; for guinea pigs, hypodermic administration, between 0.062 and 0.1 gram per kg.; for dogs, intravenous administration, about 0.012 gram per kg.

10. The fatal dose for rabbits is between 5 and 10 times as large when the alkaloids are given by the stomach as when given intravenously. Guinea pigs are more susceptible to the alkaloids than rabbits when the solutions are administered hypodermically.

11. In the treatment of the poisoning, artificial respiration was found useless. Good results were obtained with potassium permanganate, diuretin, and tea.

FIELD EXPERIMENTS WITH LUPINES.

Field experiments with domestic animals have been carried on for six years—in 1909, 1910, and 1911 at Mount Carbon, Colo., and in 1912, 1913, and 1914 at Greycliff, Mont. Two species, *Lupinus comatus* and *L. myrianthus*, were used at the Mount Carbon station. At Greycliff most of the work was done with two local species, *L. leucopsis* and *L. argenteus*, but two feedings were made with *L. leucophyllus* collected in Idaho in the Caribou National Forest. Not only were different species used, but feedings were made of different parts of the plants and also with the plants at different stages of growth.

TABLE 1.—*Summary of feeding experiments with Lupinus in 1909, 1910, and 1911 at Mount Carbon, Colo., and in 1912, 1913, and 1914 at Greycliff, Mont.*

Animals designated by an asterisk (*) preceding the serial number were given dry material, but the figures for dose are reduced to green weight, except in cases where "dry" is noted.]

Animal.		Weight of plant used.	Date of experiment.	Part of plant used (fed unless otherwise stated).	Severity of illness.	Remedy.	Result.	Pounds used for stated weight of animal.	Location from which plant used was obtained.
Designation.	Weight.								
A.—Horses given *L. myrianthus:*	*Pounds.*	*Pounds.*	1909.					*Per 1,000 pounds.*	
No. 78	600	26.5	Sept. 22 and 23	Leaves, stems, flowers, and fruit	Sick	None	Recovery	44.2	Camp.
No. 72	700	54	Sept. 22 to 26	do	Death	do	Death	77.2	Do.
No. 78	600	23.25	Sept. 25 and 26	do	Sick	do	Recovery	38.7	Do.
			1910.						
No. 78	750	33	Sept. 10 to 13	Leaves, stems, and fruit	do	Magnesium sulphate.	do	44	Castleton.
No. 78	750	81	Sept. 14 to 17	do	Not sick	None		108	Do.
			1911.						
No. 78	700	125.5	July 27 to Aug. 1	Leaves, stems, and flowers	Sick	Magnesium sulphate.	do	179.3	Do.
No. 124	1,000	158	Aug. 3 to 11	do	Not sick	None		158	Baldwin.
No. 124	1,000	234.5	Aug. 17 to 26	Seed heads	do	do		234.5	Do.
B.—Horses given *L. comatus:*									
No. 78	700	172.5	June 18 to 26	Leaves, stems, flowers, and fruit	do	do		246.4	Castleton.
No. 78	700	292	July 6 to 15	do	do	do		417.1	Do.
C.—Cattle given *L. myrianthus:*			1909.						
No. 108	430	30.5	Sept. 26 to 29	Leaves, stems, and fruit	do	do		71.43	
			1910.						
No. 620	500	45	Sept. 14 to 17	do	do	do		90	Do.
D.—Sheep given *L. comatus:*								*Per 100 pounds.*	
No. 124	90	60	June 5 to 23	Leaves, stems, and flowers	do	do		66.7	Gray's.
No. 120	83	19.75	June 23 to July 5	do	do	do		23.8	Webber Park and camp.
No. 122	96	33.75	do	do	do	do		35.2	Do.
No. 101	80 to 77	95	July 6 to 20	Leaves, stems, and fruit	do	do		119	Camp.
No. 102	86 to 85	109.5	do	do	do	do		128	Do.
No. 113	113 to 108	118.5	July 30 to Aug. 12	do	do	do		104.8	Castleton.

E.—Sheep given *L. myrianthus:*									
No. 116	100 to 90	81	July 30 to Aug. 11.	Leaves, stems, and flowers	do	do		81	Do.
No. 123	99 to 88	24.5	Aug. 13 to 24	Fruit and flowers	do	do		23	Do.
No. 105	100 to 90	55.5	Aug. 25 to Sept. 7.	Fruit	do	do		55.5	Do.
No. 119	112 to 97	19.5	Sept. 6 to 10	do	do	do		17.4	Do.
F.—Sheep given *L. comatus:*			1911.						
No. 138	121	41	June 17 to 25	Leaves, stems, and flowers	do	do		33.9	Do.
No. 139	±110	27	do	do	do	do		24.5	Do.
No. 144	103	75	June 28 to July 6	Leaves, stems, flowers, and fruit	do	do		72.8	Do.
No. 148	150	72.5	do	do	do	do		55.8	Do.
No. 146	118	101	July 8 to 19	do	do	do		85.6	Do.
No. 153	111	76	do	Leaves, stems, and fruit	do	do		68.5	Do.
No. 143	121 to 120	60.5	July 29 to Aug. 9	Seed heads	do	do		50	Do.
No. 137	153 to 146	49.76	Aug. 10 to 17	do	do	do		32.5	Do.
G.—Sheep given *L. myrianthus:*									
No. 140	94	100	July 8 to 19	Leaves, stems, and flowers	do	do		106.4	Do.
No. 150	107	15	July 25 to 28	Leaves, stems, flowers, and fruit	do	do		14	Do.
No. 156	113	7	do	do	do	do		6.2	Do.
No. 147	120 to 114	88.25	July 30 to Aug. 14	Seed heads	do	do		73.5	Castleton and Baldwin.
No. 146	121 to 115	110.5	Aug. 5 to 23	Leaves, stems, and flowers	do	do		91.3	Do.
No. 145	125 to 116	69	Aug. 19 to 30	do	do	do		55.2	Baldwin.
H.—Sheep given *L. leucopsis:*			1912.						
No. 170	79 to 65	15.75	July 13 to 27	Leaves, stems, and fruit	do	do		19.94	Greycliff station.
No. 167	71 to 62	10.5	July 16 to 27	do	do	do		14.8	Do.
No. 164	92½ to 81½	82.5	July 22 to Sept. 5	do	do	do		80.19	Do.
No. 177	50	1.5	July 30 to Aug. 2	Fruit	do	do		3	Do.
No. 180	57	1.24	do	do	do	do		2.17	Do.
No. 171	78 to 72	18.5	do	Leaves and stems	do	do		23.72	Do.
No. 176	72 to 64	13	do	do	do	do		18.05	Do.
No. 172	79½	2	Aug. 5 to 7	Fruit	do	do		2.515	Do.
No. 173	71½	1.3	do	Fruit (in corn chop)	do	do		1.82	Do.
No. 163	66½ to 52	8.5	Aug. 8 to 13	Leaves and stems	do	do		12.78	Do.
No. 175	92	1.32	Aug. 12	Fruit (drench)	do	do		1.435	Do.
No. 168	63	2.645	Aug. 14	do	do	do		4.198	Do.
No. 162	99 to 89	16	Aug. 16 to 21	Leaves, stems, and fruit	do	do		16	Do.
No. 172	78½ to 67½	19	Aug. 24 to Sept. 2	do	do	do		24.2	Do.
No. 180	59	.502	Sept. 15	Seed, unground (in oats and chop)	Death	do	Death	.85	Do.
			1913.						
No. 209	78½ to 72	.441	Aug. 15	Seed, unground (in grain)	Sick	do	Recovery	.561	Do.
No. 210	82 to 74	.220	do	Seed, ground (in bran)	Very sick	do	do	.268	Do.
No. 201	71	.385	Aug. 17	do	Death	Tannic acid (drench); gin.	Death	.542	Do.
No. 184	62½	.441	do	Seed, unground (in grain)	do	None	do	.705	Do.
No. 195	82½ to 75	.135	Aug. 19	Seed, ground (in bran)	Not sick	do		.164	Do.

TABLE 1.—*Summary of feeding experiments with Lupinus in 1909, 1910, and 1911 at Mount Carbon, Colo., and in 1912, 1913, and 1914 at Greycliff, Mont.*—Continued.

Animal.		Weight of plant used.	Date of experiment.	Part of plant used (fed unless otherwise stated).	Severity of illness.	Remedy.	Result.	Pounds used for stated weight of animal.	Location from which plant used was obtained.
Designation.	Weight.								
	Pounds.	*Pounds.*						*Per 100 pounds.*	
No. 198	73½ to 71	0.161	Aug. 19	Seed, ground (in bran)	Not sick	None		0.219	Greycliff station.
No. 203	108 to 95	.364	....do	....do	....do	....do		.337	Do.
No. 190	72 to 67	.317	Aug. 22	....do	....do	....do		.440	Do.
No. 208	84 to 86	.463	....do	Seed, unground (in grain)	....do	....do		.515	Do.
No. 211	86 to 76	.214	Aug. 23 and 24	Seed, ground (in bran)	....do	....do		.249	Do.
No. 196	75 to 68½	.319	Aug. 25 and 26	....do	....do	....do		.425	Do.
No. 185	64	.282	Aug. 31	....do	Death	....do	Death	.441	Do.
No. 202	73 to 69	.282	....do	....do	Not sick	....do		.386	Do.
No. 212	83½ to 80	.205	Sept. 2	....do	Sick	....do	Recovery	.245	Do.
No. 203	110½ to 100	.485	Sept. 6	....do	....do	....do	....do	.439	Do.
No. 196	75½ to 70	.273	Sept. 13	....do	Not sick	....do		.361	Do.
I.—Sheep given *L. argenteus:*									
No. 215	75½ to 66	.004	Sept. 3 and 4	....do	....do	....do		.006	Do.
No. 207	77 to 69	.326	Sept. 5	....do	....do	....do		.423	Do.
No. 190	71½ to 70	.245	Sept. 13	....do	....do	....do		.332	Do.
No. 210	79½ to 73	.350	Sept. 16 and 17	....do	....do	....do		.440	Do.
J.—Sheep given *L. leucophyllus:*									
No. 193	76½ to 75	.337	Sept. 15	Seed heads	....do	....do		.440	Caribou National Forest, Idaho.
No. 202	72½	.638	Sept. 18 and 19	Seed, ground (in bran)	....do	....do		.880	Do.
K.—Sheep given *L. leucopsis:*			1914.						
No. 259	116 to 107½	.384	June 8	Flower heads, young (drench)	....do	....do		.331	Station.
No. 262	84 to 80	.556	....do	Leaves (drench)	....do	....do		.662	Do.
No. 277	98½	.869	June 10	....do	....do	....do		.882	Do.
No. 280	101	.445	....do	Flower heads (drench)	....do	....do		.441	Do.
No. 292	88 to 79	.776	July 16	Fruit, fully developed (forced feeding).	Not sick (depressed).	....do		.882	Do.
No. 291	84½ to 89½	.373	July 17	....do	Not sick	....do		.441	Do.
No. 277	90 to 87	1.190	July 18	....do	....do	....do		1.322	Do.
No. 278	83½	1.473	July 19	....do	Death	Chloral and atropin.	Death	1.764	Do.
No. 238	83	1.281	July 20	....do	....do	Caffein	....do	1.543	Do.

No. 269	96½ to 95	1.383	July 23	do	Not sick	Tannic acid (drench), magnesium sulphate.		1.433	Do.
No. 240	87½ to 85	1.350	July 24	do	Symptoms	Tannic acid (drench).	Recovery	1.543	Do.
No. 297	90½ to 89½	1.297	do	do	Not sick	None		1.433	Do.
No. 256	81½	1.437	July 25	do	Death	Tannic acid (drench).	Death	1.763	Do.
No. 255	96 to 92	.992	July 28 to 29	Seed heads, fully developed (forced feeding).	Not sick	None		1.033	Do.
No. 266	88½ to 84	1.244	July 29	Pods with seed removed (forced feeding).	do	do		1.406	Do.
No. 232			July 31	Herded on lupine patch	do	do			Do.
No. 233			do	do	do	do			Do.
No. 235			do	do	do	do			Do.
No. 237			do	do	do	do			Do.
No. 240			do	do	do	do			Do.
No. 241			do	do	do	do			Do.
No. 243			do	do	Death	Atropin	Death		Do.
No. 244			do	do	Not sick	None			Do.
No. 246			do	do	do	do			Do.
No. 247			do	do	do	do			Do.
No. 250			do	do	do	do			Do.
No. 253			do	do	do	do			Do.
No. 255			do	do	do	do			Do.
No. 259			do	do	do	do			Do.
No. 260			do	do	do	do			Do.
No. 263			do	do	do	do			Do.
No. 264			do	do	do	do			Do.
No. 265			do	do	do	do			Do.
No. 267			do	do	do	do			Do.
No. 268			do	do	do	do			Do.
No. 269			do	do	do	do			Do.
No. 271			do	do	do	do			Do.
No. 272			do	do	do	do			Do.
No. 277			do	do	do	do			Do.
No. 280			do	do	do	do			Do.
No. 288			do	do	do	do			Do.
No. 290			do	do	do	do			Do.
No. 291			do	do	do	do			Do.
No. 292			do	do	do	do			Do.
No. 293			do	do	do	do			Do.
No. 294			do	do	do	do			Do.
No. 295			do	do	do	do			Do.
No. 296			do	do	do	do			Do.
No. 297			do	do	do	do			Do.
*No. 232 (dry)	74 to 73	.326	Aug. 3	Ripe pods that had shed seed (forced feeding).	do	do		.441	Do.
*No. 250 (dry)	80 to 85½	.441	Aug. 4	do	do	do		.517	Do.

TABLE 1.—*Summary of feeding experiments with Lupinus in 1909, 1910, and 1911 at Mount Carbon, Colo., and in 1912, 1913, and 1914 at Greycliff, Mont.*—Continued.

Animal.		Weight of plant used.	Date of experiment.	Part of plant used (fed unless otherwise stated).	Severity of illness.	Remedy.	Result.	Pounds used for stated weight of animal.	Location from which plant used was obtained.
Designation.	Weight.								
	Pounds.	*Pounds.*						*Per 100 pounds.*	
*No. 253	62½	1.722	Aug. 6	Pods with seed removed (forced feeding).	Death	Bled, whisky	Death	2.755	Station.
*No. 247 (dry)	109 to 103½	.721	Aug. 8	Ripe pods that had shed seed (forced feeding).	do	None		.661	Do.
No. 295	92 to 88	2.028	Aug. 10	Leaves (forced feeding)	do	do		2.204	Do.
*No. 280 (dry)	84 to 81	1.648	Aug. 11	Ripe pods that had shed seed (forced feeding).	do	do		.771	Do.
*No. 235 (dry)	82 to 76½	1.085	Aug. 14	do	do	do		1.323	Do.
No. 231	90	.298	Aug. 18	Seed (forced feeding)	Sick	do	Recovery	.331	Do.
No. 243	81	1.058	do	Leaves (forced feeding)	Death	do	Death	1.306	Do.
No. 274	28 to 26	.062	do	Seed (in bran)	Not sick	do		.221	Do.
No. 251	79 to 77	1.301	Aug. 19	Leaves (forced feeding)	do	do		1.647	Do.
No. 266	76	2.392	Aug. 20	do	Enteritis?	do		3.147	Do.
No. 250	97 to 91½	2.138	Aug. 24	do	Not sick	do		2.204	Do.
No. 274	27½ to 27½	.053	do	Seed (in bran)	do	do		.193	Do.
No. 251	80 to 75½	.353	Aug. 27	Seed (forced feeding)	do	do		.441	Do.
No. 268	83	.457	Aug. 28	do	Death	do	Death	.551	Do.
*No. 301 (dry)	81	1.653	do	Ripe pods that had shed most of seed (forced feeding).	do	Magnesium sulphate and caffein.	do	2.041	Do.
*No. 231	84 to 80	1.296	Aug. 29	Fruit, fully developed (forced feeding).	Not sick	None		1.543	Do.
No. 297	84 to 78	.463	do	Seed (forced feeding)	do	Sodium bicarbonate (repeated doses).		.551	Do.
*No. 235	92½ to 80	1.426	Aug. 31	Fruit, fully developed (forced feeding).	do	None		1.541	Do.
*No. 251	79½ to 74	1.400	Sept. 2	do	Not sick? (Possible indigestion.)	do		1.761	Do.
No. 254	90½ to 85½	.499	do	Seed (forced feeding)	Not sick	Sodium bicarbonate (repeated doses).		.551	Do.
*No. 280	84 to 78	1.597	Sept. 4	Fruit, fully developed (forced feeding).	do	None		1,901	Do.

No. 296	80 to 71	.529	....do....	Seed (forced feeding)	...do....	Sodium bicarbonate (repeated doses).		.661	Do.
No. 269	95	.733	Sept. 5	....do....	Death....	Sodium bicarbonate (repeated doses) and atropin.	Death....	.772	Do.
No. 290	88 to 88[1]	4.299	Sept. 7	Leaves (forced feeding)	Not sick..	None		4.885	Do.
No. 306	83½ to 78	3.666	Sept. 9	....do....	...do....	....do....		4.110	Do.
No. 245		(1)	Sept. 10	Leaves and stems	...do....	....do....			Do.
L.—Sheep given *L. argenteus:*									
No. 293	117 to 106	2.579	Aug. 25	Leaves, stems, and a few flowers and seed (forced feeding).	Symptoms?	....do....		2.204	Do.
No. 263	98 to 90	3.241	Aug. 27	Leaves (forced feeding)	Not sick..	....do....		3.307	Do.
No. 307	92 to 89½	4.049	Sept. 10	....do....	...do....	....do....		4.792	Do.

[1] Ate a little.

Inasmuch as nearly all the recorded losses are of sheep, most of the work was done with these animals, there being, all told, 141 experimental cases. Two head of cattle were fed, and there were 10 experiments with horses. Table 1 contains a summarized statement of the field experimental work.

EXPERIMENTS WITH CATTLE.

Two head of cattle, Nos. 108 and 620, were fed with lupine, but in neither case was there any result. This should not be interpreted, however, as proving that cattle can not be poisoned by lupine; accounts have reached the Department of Agriculture of the poisoning of cattle in the field under circumstances which make it seem very probable that lupine was the cause. However, it does not seem probable that the lupines cause any serious loss of cattle.

EXPERIMENTS WITH HORSES.

There were 10 experiments of feeding lupine to horses, 8 with *Lupinus myrianthus* and 2 with *L. comatus*. Horse No. 72, between September 22 and 26, 1909, ate, per 1,000 pounds of its weight, 77.2 pounds of lupine, including leaves, stems, flowers, and fruit. The animal died, the marked symptoms being general depression and dullness, abdominal pain, twitching of the surface muscles, and high stepping as he walked about. The animal was very much constipated and in the autopsy there was clear evidence of intestinal impaction. At the time, because of the negative results obtained, it was thought probable that the intestinal impaction was the cause of death, but a review of the case, after more complete knowledge of lupine poisoning, made it appear quite certain that this horse was a victim of lupine intoxication.

The two feeding experiments with horse No. 124 were negative. With horse No. 78 there were five feeding experiments with *Lupinus myrianthus*—two in 1909, two in 1910, and one in 1911. In 1911 there were also two experiments with this horse of feeding *L. comatus*. In four of the experiments with horse No. 78 there were distinct symptoms of illness, consisting of contractions of the surface muscles, intestinal disturbance, indicated in the main by constipation but showing diarrhea in one case, dullness and depression, with a tendency to lift the fore feet unusually high when stepping about.

The experiments with horses were sufficient to establish the fact that these animals may be poisoned by the lupines. No deductions, however, can be drawn as to the toxic dose, since the periods during which the feedings were continued were extremely variable. To establish definitely the dosage for horses would require a large number of carefully conducted experiments comparable with those on sheep, and for such experiments there has been as yet no opportunity.

EXPERIMENTS WITH SHEEP.

In the experimental work with sheep the attempt was made to have the animals, if possible, eat the plant. In experiments with seeds it was found that the extremely bitter taste led the sheep to avoid them, but when they were ground up and mixed with bran the material was eaten quite readily. When it was found difficult, in the case of corral animals, to get them to eat enough to produce any effect, drenching and forced feeding were used. In drenching, the sheep was placed on its haunches and the drench, which consisted of the plant material finely ground and suspended in water, was given by a bottle. For the forced feeding the material was ground and given by means of a veterinarian's balling gun. The plant material fed in this manner was placed a little at a time in the back part of the sheep's mouth. As soon as this was swallowed more was given, and the process continued until the desired quantity had been given to the animal.

TYPICAL CASE OF SHEEP NO. 184.

Sheep No. 184, a 2-year-old ewe weighing 62.5 pounds, was taken into the corrals on August 16, 1913, for feeding. On August 17, at 8.45 p. m., she was given 200 grams of unground seed of *Lupinus leucopsis*, mixed with oats, corn, and wheat, which was equivalent to 0.705 pound per 100 pounds of animal. During the day this was all eaten.

On August 18, at 6.55 a. m., the sheep was found lying partly on one side with her head on the ground, as though in sleep, and trembling in the forelegs. When stimulated she attempted to get up, but was unable to raise her body from the ground. Through the struggle the respiration became more marked and heavy, the animal breathing much as though in a deep sleep. After the struggle the pulse was 174 and fairly strong. At 7.10 a. m. the respiration was 36 and the temperature 101° F. Plate I, figure 1, shows the condition of the animal as she appeared at 7.15 a. m. At 8 a. m. she lay with her head extended on the ground, in much the same position as at 7.15. She raised her head for a few moments, then slowly dropped it with eyes half closed, as if in sleep. At 8.05 a. m. she held her head up, and apparently made an effort to walk. Her respiration was 36 per minute, noisy, and deep. Her sides trembled as she breathed. The pulse was 122. At 8.50 a. m. she got upon her feet and stood several minutes, then leaned against the fence and sank down again. At 8.55 a. m. she stood with her legs bent at the knees as though in an effort to balance herself. Her respiration was 36 and of the same character as before. There was some frothing at the mouth. Her ears hung low. Plate I, figure 2, shows the attitude of the animal at 8.57. At 10.30 a. m. she lay breathing as before and trembling. Her temperature was 103.3° F. At 10.35 a. m. she was raised upon

her feet and then tried to walk, but was unable to stand, and lay down again. At 10.47 a. m. she was unable to get her breath and went into a spasm, in which her legs straightened out very much as though she had been poisoned by strychnin. At 10.48½ a. m. she was breathing again more naturally. She lay upon her side, trembling violently, with her hind legs extended rigidly. At 10.50 a. m. she was quiet again. At this time she appeared to be a little bloated. At 10.52 a. m. the muscles were rigidly contracted again, and the trembling became more violent; this was followed by a spasm, in which she had great difficulty in getting her breath. At 10.55 a. m. she quieted down again, and her respiration became more regular and deep. At 10.56 a. m. another spasm came on. At 10.58 a. m. she was quiet again, with pulse 174, strong, and regular. At 11 a. m. another spasm came on, but the animal soon became quiet. At 11.08 a. m. the head was thrown back, the heart fluttered, respiration stopped, and at 11.10 a. m. the animal was dead. For several minutes before death the heart action was weak, and just before death she was unable to get her breath. The muscles gradually relaxed, the head was drawn back, and the heart stopped.

An autopsy was made upon the animal immediately, but very little abnormal was found. The heart stopped in systole, and the brain and spinal cord were congested. Other than this the animal appeared to be normal.

TYPICAL CASE OF SHEEP NO. 201.

Sheep No. 201, a ewe weighing 71 pounds, was brought into the corrals for feeding on August 16, 1913. On August 17, at 9 a. m., she was given 100 grams of ripe dry lupine seeds of *Lupinus leucopsis*, the seed having been ground in a coffee mill and mixed with 100 grams of bran. At 9.30 a. m. this material had been eaten, and she was given 100 grams more of the ground lupine seed, mixed with bran as before. At 12.20 p. m. most of this material had been eaten. Her respiration was loud and deep, as in a sleeping animal. It was estimated that the animal had eaten altogether 175 grams of lupine seed, which would be the equivalent of 0.542 pound per 100 pounds of animal.

On August 18, at 7 a. m., the animal appeared drowsy and sleepy. At 7.15 a. m. she walked about a little, throwing the forelegs out and dropping them as though lacking control. She staggered a little as she walked and appeared more sleepy than an hour earlier. There were some contractions of the surface muscles of the body. Plate II, figure 1, shows the condition of the animal at this time. At 8.15 a. m. she was still upon her feet and able to walk around, but walked as though tipsy. When standing she appeared sleepy, the ears drooped, and the eyes were half closed. She stood with her legs bent at the knees and hocks. At 9.12 a. m. she still stood with the

same sleepy look and hanging ears, and occasionally walked about in an uneasy way. There was some lack of coordination of the muscles of the forelegs. Plate II, figure 2, shows the condition of the animal at that time, and Plate II, figure 3, shows the animal about 9.30 a. m. At 11.10 a. m. the condition was about the same as at 9.12. At 11.55 a. m. the animal was found upon her knees; she got up with difficulty, but was barely able to stand upon her feet. She had been gradually growing easier, and at 12.10 p. m. was down with her head upon the ground, apparently in a sleep. At this time she was given 5 grams of tannic acid in water, and 5 minutes later 10 c.c. of gin was given in an ounce of water. At 12.20 p. m. she was found down in a corner of the corral with her head under her body. She was helped up, but fell down again on her side in a convulsive spasm. At 12.25 p. m. she lay quiet; her respiration was 32, deep and labored, and her pulse 98, strong and regular. At 12.30 p. m. an attempt was made to get her upon her belly, but she rolled over on the other side. This was repeated several times. After several attempts she lay upon her belly with her nose extended on the ground. At 12.38 p. m. she tried to get upon her feet, but was unable to do so and went over on her side. Her legs straightened out, her head was thrown back in a strychninlike spasm, respiration stopped, the eyes rolled back, and at 12.41 p. m. the animal was dead.

At the autopsy a few petechiæ were found on the walls of the ventricles of the heart. The vessels of the small intestines were injected, and the brain was slightly congested. Nothing else abnormal was noticed.

TYPICAL CASE OF SHEEP NO. 253.

Sheep No. 253, a ewe weighing 62.5 pounds, was kept in the corrals August 5, 1914, for feeding.

On August 6, at 9.20 a. m., her temperature was 102° F., her pulse 60, and her respiration 16. From 9.30 a. m. to 10.05 a. m. she was fed with the balling gun 195.31 grams of seed pods of *Lupinus leucopsis*. The pods were collected July 16, before the seeds had ripened, and allowed to dry. In the process of drying the seeds were expelled. The pods were ground and 4 ounces of water was added to facilitate the feeding. This was fed in the ratio of 312 grams of pods to 100 pounds of animal. Allowing for the loss of weight in the pods due to drying, this animal received an equivalent of 2.755 pounds of fresh pods per 100 pounds of animal weight. The sheep appeared all right during the day and was watched until 11 p. m.

On August 7, at 5.50 a. m., her temperature was 100.6° F., her pulse was 96, and her respiration 21. The animal was found lying down with her head through the fence between the boards and swinging it from side to side. Her eyes were staring and expressionless. The femoral pulse was almost imperceptible. There was no evidence

of dyspnœa. At 6.35 a. m. she was still lying upon her belly, with her head through the fence and swinging it from side to side. She was taken up and put upon her feet and walked a little distance, staggering as she walked. At 6.40 a. m. her pulse was 140, the heart beating very hard. Her temperature was 100.6° F. and her respiration 24. The animal was standing with her head lowered and swinging from side to side. She staggered across the pen, hit her head against the fence, and pushed forward, with her head partly twisted and under her body. As she lay down her head kept swinging from side to side. At 8 a. m. she was able to walk, but staggered as she moved. Her head was still swinging, pendulum fashion, from side to side. She pushed up against the side of the pen, preferably in a corner, with her head flexed toward the breast, so that at times she almost stood upon her head.

Plate III, figures 1 and 2, taken at 7.55 a. m. and 8 a. m., respectively, show the positions assumed. At 8.55 a. m. the sheep was lying quietly at the front of the pen. Her respiration was 80. She no longer swung her head from side to side and did not attempt to push it against the side of the pen. At 9 a. m. her temperature was 102.6° F., her pulse 102, and her respiration 86. The pulse was rather weak. There was some dyspnœa. She lay on her belly with her head to the left side and was quiet. At 9.15 a. m. she was up and about the corral. She would butt against the fence, then fall, extend the legs rigidly, and breathe rapidly. There was no rhythmic motion of the head at this time. At 9.40 a. m. she lay panting, with some frothing at the mouth. At 9.55 a. m. her pulse was 132, and strong in the femoral artery. Her respiration was 200, panting; her temperature was 103.2° F. She got her head into the corner of the corral and shoved forward until she almost stood upon her head. She struggled to push herself into this position, and as she was standing upon boards during the struggle her feet would sometimes slip and she would fall. After falling she would get up and start the butting process over again. At 10.35 a. m. she lay with her head to one side, the respiration being very rapid. She was disturbed, got up and started butting against the fence as before. This was kept up for two or three minutes, then she went down and remained lying with her head on one side. Plate IV, figure 1, shows her position at 10.40 a. m. At 10.55 a. m. the animal was up again and butting into the corners as before. She was drenched with 30 c. c. of whisky and an equal quantity of water. Her pulse was 132 and strong. At 11.55 a. m. she stood with her head low and part of the time on one side. Plate IV, figure 2, shows her in this position. There was a rapid chewing motion of the jaws; the motion was dorsiventral and not lateral. She bumped her head into the fence as before and

FIG. 1.—SHEEP NO. 184 AT 7.15 A. M., AUGUST 18, 1913.

FIG. 2.—SHEEP NO. 184 AT 8.57 A. M., AUGUST 18, 1913.

FIG. 1.—SHEEP NO. 201 AT 7.15 A. M., AUGUST 18, 1913.

FIG. 2.—SHEEP NO. 201 AT 9.12 A. M., AUGUST 18, 1913.

FIG. 3.—SHEEP NO. 201 AT 9.30 A. M., AUGUST 18, 1913.

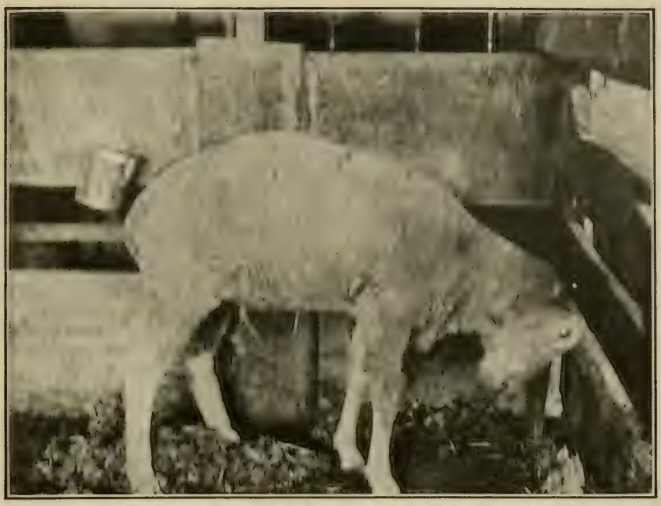

FIG. 1.—SHEEP NO. 253 AT 7.55 A. M., AUGUST 7, 1914.

FIG. 2.—SHEEP NO. 253 AT 8.00 A. M., AUGUST 7, 1914.

FIG. 1.—SHEEP NO. 253 AT 10.40 A. M., AUGUST 7 1914.

FIG. 2.—SHEEP NO. 253 AT 11.15 A. M., AUGUST 7, 1914.

staggered when she attempted to walk. At 11.22 a. m. she stood swaying from side to side. At 11.45 a. m. she was lying upon her belly with her head on one side, her respiration being about 200. At 11.50 a. m. she was up on her feet and commenced to butt into the fence again. She soon fell and lay panting. Her respiration was 160. At 11.57 a. m. she was lying upon one side and panting. At 12 noon she suddenly got upon her feet and started butting the corners, but immediately fell over, holding her head on one side. The chewing motions, as noted before, were marked. At 12.15 p. m. she got upon her feet, tried to run but fell over; she picked herself up, however, and started to butt into the corners. At 12.17 p. m. she fell down and lay quietly. At 12.30 p. m. she was on her side struggling in an attack of dyspnœa. At this time she was bled by cutting the angular artery of the eye. At 12.35 p. m. her respiration was 160. At 12.40 p. m. the movements of the jaws and lips still continued. At 1.10 p. m. she was struggling and the muscles of the flanks were trembling. Her pulse was so fast that it was impossible to count it. Her temperature was 107.6° F. At 1.11 p. m. she had fallen over on her side and was moving her body about. At 1.13 p. m. her respiration was barely perceptible, and at 1.15 p. m. it stopped. The movements of respiration and of the heart stopped at about the same time.

In the autopsy petechiæ were found upon the auricles of the heart. The lungs were congested. The walls of the ileum were injected, with some ecchymoses. The mesenteric blood vessels were injected.

LABORATORY EXPERIMENTS WITH EXTRACTS OF LUPINE SEED UPON MICE.

Preliminary experiments showed that mice are very susceptible to poisoning by extracts of lupine seed injected intraperitoneally. Accordingly, a few experiments were undertaken to determine by this method the relative toxicity of extracts of various parts of the lupine plant. Seeds, pods, and leaves of *Lupinus leucopsis* collected at Greycliff, Mont., in the summers of 1913 and 1914 were used for these experiments. The following is a description of the method used in preparing the extracts:

Material was taken from each part of the plant which it was desired to examine, and all the samples were ground in the same mill set to the same degree of fineness. They were all ground the same day and at approximately the same time. From each form of material a sample of 20 grams was taken, placed in a flask, and macerated with 150 c. c. of Prolius's solution for 48 hours. The maceration of the different samples examined was begun and ended at the same time. Ninety c. c. of Prolius's extract was then taken from each flask, filtered, and evaporated down spontaneously. The residue of each was then extracted with 1 per cent of HCl, using 3 portions. The solution was filtered off, neutralized with Na_2CO_3, and made up to 10 c. c., so that 1 c. c. of the solution was equivalent to 1.2 grams of the sample.

These extracts were made by Mr. O. F. Black, chemical biologist in the Office of Drug-Plant and Poisonous-Plant Investigations, and were used in intraperitoneal injections upon mice. Table 2 gives the results.

TABLE 2.—*Relative toxicity to mice of the various parts of Lupinus leucopsis.*

Animal.		Part of plant.	Extract used.	Plant used.		Result.
Mouse.	Weight.			Weight.	Per 25 grams of animal.	
	Grams.		*C. c.*	*Grams.*	*Grams.*	
No. 27	24	Leaves	1	1.2	1.25	Death in 7.5 minutes.
No. 35	26.5	.....do	.75	.9	.833	Death in 9.5 minutes.
No. 44	23.5	.....do	.5	.6	.64	Death in 26 minutes.
No. 47	14	.....do	.15	.18	.322	Not sick.
No. 36	26.5	Pods (seed removed)	.5	.6	.565	Death in 4.5 minutes.
No. 37	20	.....do	.25	.3	.375	Death in 6.5 minutes.
No. 45	19	.....do	.15	.18	.237	Not sick.
No. 38	15.5	Pods (seed shed)	.25	.3	.482	Very sick; recovery.
No. 43	19.8	.....do	.3	.36	.457	Sick; recovery.
No. 46	19	.....do	.35	.42	.552	Death in 11 minutes.
No. 39	24	Seed (1914 collection)	.2	.24	.25	Death in 12.5 minutes.
No. 40	19	.....do	.15	.18	.237	Sick; recovery.
No. 41	22.5	Seed (1913 collection)	.2	.24	.266	Not sick.
No. 42	21	.....do	.25	.3	.357	Death in 14 minutes.

Table 2 shows that the amount necessary to kill a mouse on the basis of the standard weight of 25 grams is approximately as follows:

	Grams.
Leaves	0.6 to 0.64
Pods (seed removed)	.3 to .35
Pods (seed shed)	.5
Seeds, collection of 1913	.3 to .35
Seeds, collection of 1914	.25

Inasmuch as it is known from other experiments that the toxic and lethal doses are practically the same, it is fair to assume that this table gives, approximately, not only the lethal dose but also the toxic dose. From Table 2 it appears that the seeds collected in 1914 were slightly more toxic than those collected in the preceding year. Possibly a certain amount of the toxicity was lost in keeping. It appears also that the pods from which the seed had been shed were only about half as toxic as the seed. The pods from which the seed had been removed were considerably more toxic than the pods from which the seed had been shed, and the leaves were only about one-half to one-third as toxic as the seed. These figures do not conform very closely to those obtained in the field experiments upon sheep, but perhaps as closely as could be expected under the different conditions of experimentation. An especially interesting feature of this experiment was the definite proof obtained by Mr. Black by analytical methods of the presence of the alkaloids in the leaves, with the consequent deduction, confirmed by actual experiments,

that the leaves are toxic. Inasmuch as the field experiments upon sheep were inconclusive in regard to the toxicity of the leaves, this is an important addition to the knowledge of the subject.

The field experiments gave little information as to the relative toxicity of the different species of lupines. There was nothing to indicate any difference in the toxic effect of those used in the feeding experiments. Accordingly, a few experiments were made on mice with extracts of the seed of the available species. Seeds of three American species were used, and through the kindness of Mr. Piper, of the United States Department of Agriculture, seeds were obtained of the three common European species, *Lupinus albus*, *L. angustifolius*, and *L. luteus*. Extracts of these lupines were prepared by Mr. Black, using exactly the same method as that employed in the preceding test of the seeds of *L. leucopsis*. A series of tests was made on mice by intraperitoneal injection of these extracts. Table 3 shows the results. In this table, for purposes of comparison, the experiments with seeds in Table 1 are included.

TABLE 3.—*Comparative toxicity to mice of the seed of different species of lupines.*

Plant.	Animal.		Amount used.		Used per 25 grams of animal.		Result.
	Mouse.	Weight.	Extract.	Plant.	Extract.	Plant.	
Lupinus leucopsis:		*Grams.*	*C. c.*	*Grams.*	*C. c.*	*Grams.*	
1914 seed	No. 39.	24	0.20	0.24	.....	0.25	Death in 12½ minutes.
Do	No. 40.	19	.15	.18	.....	.237	Sick; recovery.
1913 seed	No. 41.	22.5	.20	.24	.....	.266	Not sick.
Do	No. 42.	21	.25	.3	.....	.357	Death in 14 minutes.
Lupinus luteus	No. 49.	18.5	.15	.18	0.2	.25	None.
Do	No. 49.	.....	.5	.6	.7	.8	Sick; recovery.
Do	No. 50.	21	.25	.3	.3	.36	Symptoms.
Lupinus albus	No. 51.	23	.5	.6	.54	.65	Death in 3 minutes.
Do	No. 52.	23.5	.2	.24	.21	.25	Death in 13 minutes.
Lupinus angustifolius.	No. 53.	24	.25	.3	.26	.3	Death in 19 minutes.
Do	No. 54.	27	.15	.18	.14	.17	Symptoms.
Lupinus leucophyllus:							
1913 seed	No. 56.	22.5	.25	.3	.....	.335	Death in 6½ minutes.
Do	No. 57.	21.5	.15	.18	.....	.2075	Symptoms.
Lupinus argenteus:							
1913 seed	No. 58.	21.5	.25	.3	.....	.35	Death in 4 minutes.
Do	No. 59.	26.75	.15	.18	.....	.168	Death in 6 minutes.
Do	No. 60.	19	.75	.09	.....	.1185	Symptoms.

In regard to mouse No. 49, it should be stated that inasmuch as the first injection of 0.15 c.c. of extract produced no results, a second injection of 0.5 c.c. was given shortly afterward. From the known facts in regard to lupine poisoning it is not to be presumed that there was any appreciable accumulative effect from the preceding injection. Table 3 shows very clearly that by this method of experimentation *Lupinus albus* and *L. angustifolius* appear to be about equally toxic. *L. luteus*, however, is much less toxic, it being necessary to take probably three or four times the quantity in order to produce results. It

may be noted in passing that *L. luteus* is the species which is said to be responsible for the so-called ictrogenic poisoning which occurs in northern Germany. In regard to the American species, *L. leucopsis* and *L. leucophyllus* are about equally toxic and do not differ much from *L. albus* and *L. angustifolius*. *L. argenteus* appears to be much more toxic than the other American species examined.

It should be noted that in these experiments on mice the animals died of respiratory paralysis, with marked dyspnœa, the heart sometimes continuing to beat as much as a minute after respiration had ceased. The work with extracts is of a preliminary character, and it is intended to prepare for future publication an extended study of the alkaloids and the effect of the extracts.

PART III.—DISCUSSION AND GENERAL CONCLUSIONS.

FAILURE TO POISON SHEEP IN 1910, 1911, AND 1912.

In the early work of the field experiments it was assumed that the lupines were sufficiently toxic to poison animals in the course of ordinary feeding. It was thought that if the animals were confined and given little or nothing of other food material and were abundantly supplied with lupine, symptons would appear if the plants were toxic.

There was little in American literature to indicate the probable dosage. Chesnut and Wilcox (1901, p. 108) state that 150 pods were fed to each of two sheep and both were fatally poisoned. Accordingly, in 1910 the sheep used were confined in corrals and were fed all they would eat. One animal, sheep No. 102, between July 6 and 30, ate 128 pounds of lupine tops, including leaves, flowers, and fruit, and another, between August 25 and September 7, ate 55.5 pounds of seed-containing pods, with no ill effects other than a loss of weight. Sheep No. 105, which received the 55.5 pounds of pods and seeds, was given on some days as much as 8 pounds.

The experience of 1911 was similar and with no more results. Although a large number of experiments were made in 1912, in only one case were there harmful results. This animal, sheep No. 180, was fed 0.85 pound of lupine seeds on September 15, and the next day it was found dead in the pasture. At that time, because of the large number of negative experiments, it was thought that the death of the animal must be due to some other cause than lupine poisoning. The more complete knowledge of the effect of lupine, brought out in the work of 1913 and 1914, makes it evident that this was a case of lupine poisoning. All the other cases of 1912 were negative.

In comparing the work of these years it will be noticed that in 1913 the feeding of seeds was done in a single day, and in most cases the quantity fed was eaten in a short time. This was true of sheep No. 180 in 1912, which ate the given quantity within an hour. In

1914 the experiments were by forced feeding, so that the animal received the total quantity in a short period of time; while in 1910 and 1911 some of the animals received large quantities, but the feeding was distributed over a long period. Although in some cases as much as 8 pounds was fed in a single day, this was eaten in a more or less leisurely way.

In 1912 two sheep, Nos. 175 and 168, were drenched with the fruit, No. 175 receiving 1.435 pounds and No. 168 4.198 pounds, and showed no symptoms, although the 1914 experiments indicated that the toxic dose of fruit is about 1½ pounds. Sheep No. 175, however, received its lupine in three doses, between 10.30 a. m. and 3.30 p. m.; it is possible that this animal might have been poisoned had it received the material in a single dose, as the quantity given was close to the toxic limit. But sheep No. 168 received 4.198 pounds, between two and three times the toxic dose as determined in 1914; this material was given in six doses, between 8 a. m. and 7 p. m. It seems probable that the only reason this animal was not poisoned was because of the length of time during which the material was given.

It appears to be a fair inference that the excretory apparatus of the sheep can take care of the toxic substance of the lupine provided the quantity given at any one time does not reach the toxic limit. It is hoped to carry on later detailed experiments to show just how this is done—experiments for which adequate facilities have not been available thus far. It is probable, however, that this excretory work is done largely by the kidneys, since preliminary experiments with other toxic substances upon sheep indicate that the kidneys are very efficient in the removal of some toxic substances. It has also been shown by others that the lupine alkaloids are found in the urine. The failure to get results in the earlier experiments was due to the fact that the sheep did not get at any time more than the excretory apparatus could remove before the toxic limit was reached.

LUPINE NOT A CUMULATIVE POISON.

The lupines as poisonous plants do not have a cumulative effect. This has an important bearing on range management of sheep, for it is evident that sheep may graze continuously on lupines with no bad results, provided the toxic limit is not reached at any one time. Inasmuch as the toxic dose is a fairly large quantity, and sheep do not ordinarily show any special fondness for the lupines, well-fed animals are not likely to be poisoned by lupines. It is only when, for some reason, they eat an unusually large quantity that losses occur. This is discussed in more detail under "Range conditions under which sheep are poisoned" on page 39.

TOXICITY OF DIFFERENT SPECIES OF LUPINE.

The field experiments give little information as to any difference in toxicity between the species of lupines. While only one of the two species used in the experiments with horses produced effects, viz, *Lupinus myrianthus*, the feedings of *L. comatus* were not conducted under exactly the same conditions, the period of feeding being considerably longer than in the experiments in which poisoning was produced by *L. myrianthus*.

The probable reasons why sheep were not poisoned on *Lupinus myrianthus* and *L. comatus* are discussed on page 28. Nearly all the experiments at Greycliff were on *L. leucopsis*. The field experiments on *L. argenteus* and *L. leucophyllus* were so few that it is not safe to make any deductions. It seems probable that in the experiments of feeding the seed of *L. argenteus*, the dosage was just a little too small, even granted that the plant is equally toxic with *L. leucopsis*.

The experiments with mice detailed on pages 25 to 28 indicate that the European species, *Lupinus albus* and *L. angustifolius*, are about equally toxic with *L. leucopsis* and *L. leucophyllus*, while *L. luteus* is much less toxic, the dosage probably being at least three times as great as that for the other species. Inasmuch as the experiments on mice were few in number, too much importance must not be attached to the results. They are interesting, however, as giving some indication of the probable comparative toxicity of the species examined. These experiments with mice give an indication of the probable toxicity of the leaves as compared with other parts of the plants.

TOXICITY OF LUPINE LEAVES FOR SHEEP.

Sheep No. 243 was an undoubted case of lupine poisoning. The symptoms were typical and it received only leaves. It was impossible, however, to verify this by other experiments. The other animals (Nos. 295, 266, 256, 290, and 306, with *L. leucopsis*, and Nos. 263 and 307 with *L. argenteus*) were fed much more, in some cases more than three times as much, without any effect whatever. It should be added that while all animals upon the range apparently graze upon lupine with impunity, sometimes eating very large quantities, there are cases when it seems probable that lupine leaves must be toxic. For example, cases of undoubted lupine poisoning in the Absaroka National Forest, examined by Dr. Hadleigh Marsh in the summer of 1914, apparently did not have an opportunity to obtain enough of the seeds to cause the difficulty. If it could be assumed that the leaves are sometimes toxic, these cases would be much more easily explained. Many similar cases of range poisoning have occurred where it was difficult to explain the loss except by assuming

that the lupine leaves are toxic. Moreover, laboratory work, conducted with the assistance of Mr. O. F. Black, shows clearly that there is a large quantity of the alkaloid in the leaves, although less than in the seed.

A careful analysis of the cases of sheep fed with leaves offers no explanation for the difference in results, although many possible factors have been taken into consideration, such as difference in animals, difference in methods of administration, seasonal change of toxicity, etc. All that can be said at this stage of the investigation is that while lupine leaves are not always injurious they are toxic, and under some conditions—conditions which can not now be defined—they cause illness and death. It is evident that no definite statement can be made as to the toxic and lethal dose of leaves for sheep.

TOXICITY OF LUPINE SEED FOR SHEEP.

Table 4 is a statement of the sheep poisoned by lupine seed in 1913, showing the quantity in each case which produced the result.

TABLE 4.—*Sheep poisoned by lupine seed in 1913.*

Feed and animal.	Date fed.	Pounds fed per 100 pounds of animal.	Result.
Unground seed:			
No. 209	Aug. 15	0.561	Sick; recovery.
No. 184	Aug. 17	.705	Death.
Ground seed:			
No. 210	Aug. 15	.268	Sick; recovery.
No. 201	Aug. 17	.542	Death.
No. 185	Aug. 31	.441	Do.
No. 212	Sept. 2	.245	Sick; recovery.
No. 203	Sept. 6	.459	Do.

Inasmuch as sheep No. 208 received 0.551 pounds of the unground seed without any toxic effect, it would appear that the dose received by sheep No. 209 (0.561 pound) with resulting illness, must have been very near the toxic limit. As the only sheep that died (sheep No. 184) received 0.705 pound, the lethal limit, so far as these experiments show, lies between 0.561 and 0.705 pound.

When ground seed was used, the dosage was much smaller, as would be expected. Sheep No. 212 was poisoned by 0.245 pound, and sheep No. 210 by 0.268 pound. Others were fed larger quantities without effect; for example, sheep No. 196 received 0.425 pound, and sheep No. 207, 0.423 pound, while several received 0.3 pound or more. Sheep No. 196, however, received its dose in 2 days, whereas the others received theirs in a single day. It seems that sheep may be poisoned on as little as 0.25 pound or may receive as much as 0.423 pound without effect.

The two cases of death resulted from doses of 0.543 and 0.441 pound. The general deduction from the experiments of 1913 on ground seed was that the toxic dose was between 0.25 and 0.5 pound, and the lethal dose about 0.5 pound, with the probability that in the average cases the lethal dose was somewhat more, perhaps nearly 0.6 pound.

It was considered that these experiments determined the dosage nearly enough for practical purposes, and in the experiments of administering ground seed in 1914, which were mainly with reference to the effect of antidotes, the dosage was intended to be heavy enough to produce serious illness, if not death. The general results showed that the estimate of dosage made in 1913 was approximately correct, and that the toxic dose is somewhat less than 0.5 pound, sometimes as low as 0.25 pound.

TOXICITY OF LUPINE PODS FOR SHEEP.

The number of experiments of feeding lupine pods was not sufficient to determine the dosage with any exactness. Sheep No. 253 died on August 6, 1914, from eating 2.755 pounds of pods. This material had been collected previously and dried, but the weight as given is the green weight, as the loss from evaporation was known. These were pods in which the seed was not yet ripe.

Sheep No. 301 died on August 28, 1914, from eating 2.041 pounds of pods which were collected after they had shed most of their seed; a few seeds, however, remained attached to the pods. The weight given is the dry weight, as there was no way of estimating the loss of water in drying. In all the other cases much smaller quantities were fed, and no intoxication resulted. It can only be said that the pods are distinctly toxic, but the dosage is much greater than of the seeds.

It may be added in this connection that in 1913 a careful computation was made of the relative weights of the seeds and pods in the fruit, and that, based on the result of this work, the toxic dose of pods would be 3.4 pounds. Without much doubt the toxicity of the pods varies at different seasons and probably is much reduced in the dried pods remaining attached to the plants in the late summer and fall.

TOXICITY OF LUPINE FRUIT FOR SHEEP.

By "fruit" is understood the pods with the contained seeds. A considerable number of experiments were made to determine the toxicity of the fruit as compared with the seed. Table 5 gives the results of these experiments. The term "Seed heads" means the fruits and the stems bearing them. In the cases listed under "Fruit, fully developed," the pods were picked from the stems.

The last four feedings under "Fruit, fully developed" were of very poor, locoed animals; consequently, the dosage (as computed

according to weight) would be distinctly different from that computed for the same animals in a normal, healthy condition. This may possibly explain why in the cases of Nos. 251 and 280 the dosage, computed on the basis of a 100-pound animal, so much exceeds the lethal dose shown in the preceding experiments. For example, sheep No. 280 weighed 99 pounds earlier in the season, while at the time of the experiment it weighed only 84 pounds. If the dosage of material given September 4 were computed on the assumption that the animal had its original weight, it would reduce the amount given in the table to approximately the toxic or lethal dose of the preceding animals, and as the margin between no symptoms and toxicity is so small this animal would not differ materially from the others.

TABLE 5.—*Sheep given forced feedings of lupine fruit in 1914.*

Feed and animal.	Date fed.	Pounds fed per 100 pounds of animal.	Result.
Fruit, fully developed:			
No. 292	July 16	0.882	Not sick.
No. 291	July 17	.441	Do.
No. 277	July 18	1.322	Do.
No. 278	July 19	1.764	Death.
No. 238	July 20	1.543	Do.
No. 269	July 23	1.433	Not sick.
No. 240	July 24	1.543	Symptoms.
No. 297	do	1.433	Not sick.
No. 256	July 25	1.763	Death.
No. 231	Aug. 29	1.543	Not sick.
No. 235	Aug. 31	1.541	Do.
No. 251	Sept. 2	1.761	Do.
No. 280	Sept. 4	1.901	Do.
Seed heads, fully developed:			
No. 255	July 28-29	1.033	Do.

It is evident from Table 5 that approximately 1½ pounds of fully developed fruit will produce symptoms or death in a 100-pound sheep—that is, it takes three times as much of the fruit to poison as of the seed.

SYMPTOMS.

Some of the sheep poisoned by lupine, froth at the mouth, but this is by no means a universal symptom. The most noticeable and significant symptom is the character of the breathing. In the milder cases the breathing is heavy and labored, subsiding into a condition of coma in which the animal may continue for a long time, snoring as though in a deep sleep. If able to stand, the animal may fall over in its sleep. In the more acute cases, there are severe attacks of dyspnœa, during which the animal throws itself about violently in its attempts to breathe. During these attacks the tongue and mouth become cyanotic from the congested peripheral blood vessels. Sometimes in these attacks of dyspnœa the animal dies in convulsions in which the limbs are extended rigidly, much as when poisoned by strychnin. In other cases the condition of coma deep-

ens until the animal dies without a struggle. The convulsive attacks of dyspnœa, however, may be considered typical of lupine poisoning. Drooping of the ears is noticeable in the early stages of the poisoning. In many cases the poisoned animal is continually pushing its head against surrounding objects. In corral cases the sheep pushes against the fence, lowering its head so that sometimes the animal almost stands on its head. These attitudes are shown in Plate III, figures 1 and 2. If moved from one point it may immediately push up against the fence in another place, sometimes throwing its head through an opening and remaining in that position. Sometimes the head will be swung rhythmically from side to side.

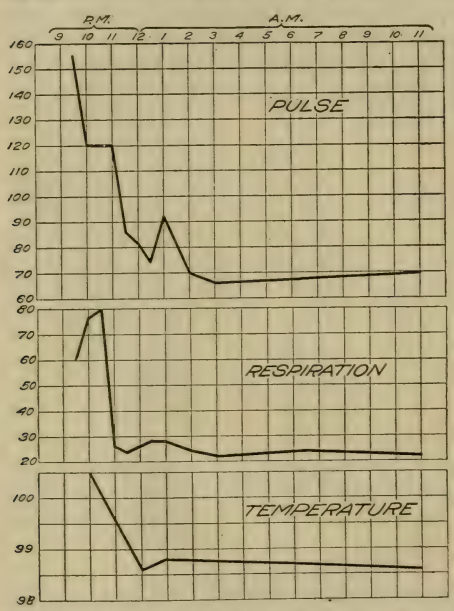

FIG. 2.—Curves showing the changes in pulse, respiration, and temperature of sheep No. 185.

Generally when sheep become affected on the range they run about in a frenzied way, butting into other animals and objects. Handling the animals under such conditions excites them to such an extent as seriously to interfere with their chances of recovery. When attempts were made to administer remedies by drenching, it was found that the animals lost more by the increased excitement than they gained from the remedy. If the sheep does not die in the period of excitement, it staggers until it falls, then lies in a stupor, which in the fatal cases gradually grows deeper.

The pulse and respiration are very high in the acute stages of the intoxication, but later are not very different from normal, except that the pulse rate is frequently increased just before death.

The intoxication produces no effect on the temperature, but in long-continued cases the temperature gradually falls, sometimes to between 98° and 99° F. The curves (fig. 2) showing the changes in

the rate of the pulse, respiration, and temperature of sheep No. 185 are fairly typical of the changes which ordinarily take place.

Associated with the condition of excitement there is frequently more or less violent trembling. Nausea is not often exhibited. Bloating occurs in some cases, probably being more likely to occur when the sheep eat very largely of lupine leaves.

Especially characteristic of lupine poisoning are: (1) Excitement, leading to running about and butting into other objects; (2) convulsions, accompanying the attacks of dyspnœa; and (3) heavy breathing, sometimes accompanied by snoring.

There is considerable variation in the length of time which elapses between the feeding of lupine and the incidence of symptoms of poisoning. In some cases symptoms appeared in 1 or 2 hours, while there were other cases in which nearly 24 hours passed before symptoms were noticed. It is evident that rumination does not necessarily precede the symptoms; in fact, there was no evidence that rumination occurred in any of the experimental sheep, although as they were not under constant observation it could not be said positively that rumination never took place.

It can be seen from the experimental work that sheep upon the range, when poisoned by lupine, may not exhibit symptoms until they have left the source of their trouble far behind.

In the autopsies, the peripheral blood vessels were found strongly congested. The left heart was usually strongly contracted, and upon the surface of the heart in most cases were petechiæ. The lungs were congested, and sometimes the liver. The blood vessels of the brain were somewhat congested, and generally the blood vessels of the inner wall of the ileum were more or less congested.

The immediate cause of death is evidently respiratory paralysis. Death may follow very quickly after the first symptoms, or the animals may live for 2 or 3 days.

As noted in the description of the experiments of intraperitoneal injection of lupine extracts in mice, the animals died of respiratory paralysis, showing symptoms which were comparable with those exhibited by sheep.

The preceding details of symptoms are those exhibited by sheep. The experiments with horses were so few that no complete picture can be given. The distinct symptoms noted were twitching of the surface muscles, constipation, dullness, and a tendency when walking to lift the fore feet high.

Dr. A. D. Knowles, of Butte, Mont., has recently treated some interesting cases of lupine poisoning of horses. Dr. Knowles has made a very careful study of these cases and has done some experimental feeding, making autopsies and having microscopic preparations made of the diseased organs. These horses exhibited symptoms

comparable with the "ictrogenic" poisoning reported in Germany, especially noticeable being the atrophy of the liver accompanied by a yellowing of the connective tissues.

While some American authors have distinguished between "acute" and "chronic" lupine poisoning, their statements appear to have been drawn from European sources, and Dr. Knowles has apparently been the first to note and record definitely cases which can be diagnosed as instances of "lupinosis" or ictrogenic poisoning. The clear-cut evidence presented by Dr. Knowles seems conclusive and makes it probable that other similar cases will be found, although it does not seem likely that lupine causes large losses of horses in the aggregate.

PATHOLOGY.

Some typical pathological material from the autopsies was examined by Dr. Formad, of the Bureau of Animal Industry. A large amount of material remains for examination, which may be made the subject of a future report. The general character of the preliminary report was confirmatory of the results of the macroscopic examination of the cases.

There was fullness and congestion of the pulmonary capillaries.

The hepatic cells showed the presence of a mild degree of cloudy swelling and some œdema.

The kidneys showed a slight degree of cloudy swelling of the epithelium, and in some cases fullness between the convoluted tubules of the cortex and overdistension of the capillaries of the medulla accompanied in places by outwandering of the leucocytes and diapedesis of the red-blood corpuscles, indicating a marked congestion.

COMPARISON OF "LUPINOSIS" AND POISONING OF SHEEP BY AMERICAN LUPINES.

The symptoms of lupinosis are described in detail by a number of European authors, e. g., Zürn (1879), Arnold and Schneidemühl (1883), Roloff (1883). Summaries are given by Dammann (1902, p. 340–341) and Hutyra and Marek (1913, p. 524–525).

The characteristic symptoms are:

(*a*) Loss of appetite.
(*b*) Fever in the first stages of the disease.
(*c*) Weakness.
(*d*) Cerebral excitement; thrusting the head against a wall and into corners.
(*e*) Gnashing of teeth.
(*f*) Pain in hind part of body.
(*g*) Diarrhea; ill-smelling excrement.
(*h*) Sometimes bloody urine, containing bile and albumen.
(*i*) Yellowing of conjunctiva and visible parts of mucous membranes in most cases, but not in all.
(*j*) In some cases swelling of ears, eyelids, lips, and nose.

(*k*) In autopsies there is seen a citron-yellow color of the body tissues, hemorrhages in various parts of the body, especially in the mucous membranes of the alimentary canal, the peritoneum, omentum, mesentery, the epicardium and endocardium, frequently fullness of gall bladder, generally an acute yellow liver atrophy, while in other cases the whole picture presents an appearance of acute phosphorus poisoning.

The German authors distinguish between acute and chronic cases, the symptoms being the same, but in the latter the liver exhibits chronic interstitial inflammation, leading to atrophy of the organ, this being accompanied by nephritis and enlargement of the spleen.

It will be noticed that the laboratory results obtained by Sollmann and by Clawson and Black agree very well with the field experiments with sheep, but differ very distinctly from the symptoms of lupinosis. The fever and jaundice which are especially characteristic of lupinosis have never been observed in sheep in America, either in experimental feeding or in poisoning upon the range. It must be concluded that ictrogen is not the cause of loss of sheep on the ranges of the United States, but that the poisoning is due to the alkaloids in the lupines.

The symptoms in the corral experiments and in range cases are distinctly those of alkaloidal poisoning. The question naturally arises as to the explanation of the difference between the poisoning of animals as exhibited in Germany and in the United States. The lupines examined in Germany possess alkaloids which are similar to those found in the American lupines, if not identical with them, and yet few clear cases of alkaloidal poisoning of domestic animals have been reported, while in America there has been no poisoning from ictrogen. In the absence of any determination of what ictrogen really is or how it is formed, only a hypothetical explanation can be given. If it is granted that ictrogen is the cause of lupinosis and if the opinion is accepted, which seems to be held by the later authors, that ictrogen is formed by the action of microorganisms upon the lupine, a possible explanation lies in the different conditions of the countries. The European lupines are cultivated plants, grown and handled like hay. The poisoning cases are caused by lupine that is exposed in the mass, and sometimes under conditions favorable to the growth of microorganisms. The American lupines are wild plants, which grow in a somewhat scattered manner; they are not collected in masses, and consequently do not have an especially favorable environment for the growth of microorganisms. Moreover, it is very possible that the particular organisms which produce the toxic substance in Europe are not present in this country; of this nothing can be said positively, for no one has yet been able to demonstrate that any specific organism or group of organisms is responsible for the hypothetical substance ictrogen. Therefore, on the supposition that there is such a substance as ictrogen, or lupino-

toxin, it seems possible that it would not be produced in America, at least under range conditions.

The fact that there is so little evidence that domestic animals in Europe suffer from the alkaloids of lupine may be explained by the different way in which the animals are handled. It is shown elsewhere in this paper that lupine poisoning of sheep on the western ranges is ordinarily associated with deficiency in the food supply. Rarely, if ever, are well-fed sheep poisoned. It may be assumed that the sheep in Germany that feed upon the lupine are stall-fed or pasture-fed and eat somewhat at leisure, so that seldom would they be likely to reach the toxic limit in a single feeding. In this connection, however, it may be noted that some of the symptoms mentioned by the German authors resemble those of alkaloidal poisoning, and, granted that ictrogen is the principal cause of the losses, it is possible that there is a certain amount of alkaloidal poisoning in addition. This would account for the nervous symptoms described by the German authors, for these correspond to the phenomena exhibited by western sheep suffering from the lupine alkaloids.

It should be noted in this connection that the work of Dr. Knowles mentioned on page 35 seems to show that under some conditions ictrogenic poisoning of horses may occur in America.

The exact relationship between poisoning by lupine alkaloids and ictrogenic poisoning is far from clear, and it is to be expected that the chemical investigations which are now being carried on by the United States Department of Agriculture will aid in clearing up this subject.

REMEDIES.

It was hoped that some remedy might be found by which recovery from lupine poisoning might be aided, but the results of the experimental work in this direction were disappointing. Whisky, gin, and atropin were tried, with no beneficial results. Caffein and Epsom salts were used to increase excretion, but without any advantage. Tannic acid and sodium bicarbonate were used as antidotes. In the publication on Zygadenus,[1] there is a discussion of reasons why the use of antidotes in a drench in any ordinary method of administration should not be expected to be beneficial. As in the work on Zygadenus, experiments were made of giving sodium bicarbonate in frequently repeated doses. This was tried in four cases (sheep Nos. 297, 254, 296, and 269). Sheep No. 269 received 0.772 pound of seed and died in spite of the remedy, but sheep No. 296 received 0.666 pound, considerably more than the toxic dose, and was not sick. This animal received the sodium bicarbonate every half hour, while sheep No. 269 received it at hour intervals. There seems to be little doubt, as in Zygadenus poisoning, that if the sodium bicarbonate

[1] U. S. Dept. of Agr. Bul. No. 125, p. 41.

can be administered at intervals frequent enough to catch the toxic principle as it enters the fourth stomach, recovery may be aided. This is of considerable theoretical interest, and the method might be used in order to save an especially valuable animal, but, of course, range animals can not be treated in this way, for the herder may have a large number of sheep sick at the same time. It is not unusual for 200 or 300 cases to occur suddenly, and any remedy which involves the administration of more than one or two doses is useless.

Herders frequently bleed sheep poisoned by lupine and claim good results. There seems no logical reason for this, however, and the experience of the writers at the field station leads them to consider bleeding as harmful rather than beneficial.

RANGE CONDITIONS UNDER WHICH SHEEP ARE POISONED.

It must be recognized that corral experiments, while superior to laboratory work in unraveling the complex problems of plant poisoning of domestic animals, do not cover the conditions of range poisoning. It is sometimes very difficult to decide to what extent the results of intensive corral feeding can be used in the explanation of range phenomena. Laboratory and corral experimentation are, of course, essential in such a study, and may give, in fact do give, fundamental information. An intimate acquaintance with range conditions is, however, necessary for the practical elucidation of these problems. Such an acquaintance with range conditions is somewhat difficult for the scientific investigator to acquire. Sheep are grazed in locations situated at long distances from regular avenues of travel or communication, and they are also moving from place to place. Cases of poisoning are reported, perhaps, some days after the trouble has occurred, and investigation at that time is likely to be useless. It is very difficult for the investigator so to locate himself as to be able to see these cases when they occur. These difficulties doubtless explain why there has been so little exact knowledge of the conditions surrounding the losses. There has been, moreover, no way of placing a correct valuation on the reports made by sheep herders and owners. The average sheep herder does not have a high order of intelligence, and this has led to an underestimate of the testimony of these men, for the fact has been overlooked that many of them are keen observers with a practical knowledge of conditions far superior to that of the average scientific investigator. The writers of this paper have had long and intimate acquaintance with the western stock ranges, but they have frequently been put to shame by the wonderful, almost instinctive, readiness with which an experienced sheepman will unerringly recognize slight symptoms of disease in the members of his flocks. The writers were fortunate in being able to observe many

range cases, and the conditions under which poisoning may occur seem now quite clear.

It was early recognized that lupine poisoning ordinarily occurs only when hungry sheep graze upon the plants. Well-fed bands are rarely, if ever, poisoned. This statement, it may be said in passing, can be made general and covers practically all poisonous plants. If sheep are taken from the cars and turned into a pasture abundantly supplied with lupine, disastrous results are likely to occur. In July, 1914, 400 sheep, out of a band of 4,000, were lost near Lakeview, Oreg. The matter was investigated by Mr. Norman G. Jacobson, of the Forest Service, who found that the sheep had been driven 34 miles in four days with a scarcity of forage. On July 25, after a day's drive of 10 miles, they were turned into a 10-acre pasture which, investigation showed, contained little but sagebrush and lupines, and the lupines were in pod. The sheep, of course, ate the lupines and with resulting loss. Many losses have occurred in the fall when sheep are coming down from the mountain ranges and have been caught by snow. On such occasions the fall of snow may cover the grasses, but leave the lupines exposed. Hungry sheep coming upon such an area may eat enough of the lupines to produce poisoning. In the fall of 1913 a sheep owner in Montana lost 300 sheep in this way.

An area in the Caribou National Forest was investigated where annual losses have occurred. It was found that the sheep coming from the mountains pass through thick patches of lupine and eat it greedily. The fact that the lupines are in pod at the time of the drive makes the matter worse. In 1911, an especially disastrous year, one outfit lost 1,000 head in this locality.

And yet, in spite of these known cases of severe loss, sheep sometimes graze on lupine through a good part of the season and with no harm. Except as they are especially hungry sheep rarely, if ever, eat enough of the lupine to cause trouble. Poisoning is much more likely to occur if sheep are hurried over a lupine area, for then in their eagerness and jealousy of each other they seize upon the lupines, which are more easily reached than the grasses. Generally speaking, it is much better to drift sheep over a lupine area than to drive them. It may be noted that sheep that are new to a locality are much more likely to eat too much of the lupine than those that are accustomed to the country.

An attempt was made in 1912 to demonstrate in an experimental way that hungry sheep may be poisoned when they feed upon lupine. A bunch of 11 sheep were kept without food for 36 hours and then, during one day, were driven 12 to 15 miles with very little opportunity to eat. About 5 p. m. they were brought to a thick lupine patch and allowed to graze. They fed until about 8.30 p. m., when they

were bedded down. They were up and feeding again at 12.15 a. m. and were grazing most of the time until 6.30 a. m., with the exception of the hour from 4 to 5. To the disappointment of the observers none of the animals was poisoned. It was noticed, however, that while a good deal of lupine was eaten they did not take to it greedily and preferred the grass, which was in fair abundance.

In thinking over the experiment later, it seemed probable that the fact that the sheep were allowed to feed freely, combined with the abundance of grass, might explain the lack of results. It was therefore decided to repeat the experiment with the difference that the sheep should not be allowed to feed freely upon a lupine patch, but should be kept moving back and forth, the idea being that in this way they might snatch at the lupine as the most prominent plant. An experiment of this kind was tried July 31, 1914. Thirty-six sheep were corralled at night and kept in until 2 p. m. the next day with no food. At 2 p. m. they were driven about a mile to a lupine patch having an abundance of pods and seed. It proved to be an unfavorable time for such an experiment, for it was very hot and the sheep would not feed until about 7 p. m. They grazed until about 8 p. m. and were kept on the move all this time. They were driven back to the corrals. The time of grazing was so short that it was assumed the experiment was a failure, and the sheep were not observed during the night. The next morning sheep No. 241, which had been observed as one of those eating the most lupine, was found down, and a little later it died, the symptoms and autopsy indicating that it was, without doubt, a lupine victim. The outcome of this experiment was considered to be a confirmation of the general explanation of range poisoning as given before.

TREATMENT OF RANGE ANIMALS TO AVOID POISONING.

From what has been said of the conditions under which range poisoning occurs, it is evident that much of the loss can be prevented by proper management of the bands.

Sheep should never be taken from the cars to a pasture having much lupine. It is cheaper to buy hay. After long drives with insufficient forage avoid grazing grounds which are covered with lupine. If it is necessary to drive sheep over lupine patches, do not hurry them, but allow them to spread out and drift across. Special care should be taken in the fall, when the grass may be covered by a fall of snow. In the treatment of the flocks remember the general fact, which is applicable in regard to all poisonous plants, that well-fed sheep are not likely to eat injurious plants. Conditions under which sheep get ravenously hungry should, if possible, be avoided.

Herders should recognize the fact that the pods and seeds are especially poisonous and that, consequently, poisoning is more likely to

occur at the time when the plants are in fruit and in seasons when the fruit is most abundant. In very dry seasons frequently little fruit is matured, while a wet season, especially a wet spring, may cause a heavy production of fruit.

SUMMARY.

(1) Lupines have been cultivated and used from the time of the ancient Greeks and Romans, but their poisonous properties have been recognized only in very modern times. Heavy losses of domestic animals were reported in northern Germany in 1872 and the succeeding years.

(2) While chemists have shown the presence of poisonous alkaloids in the lupines, the losses in northern Germany have been considered by investigators as due not to the alkaloids but to a hypothetical substance known as ictrogen.

(3) An investigation by Dr. Sollmann showed the presence of alkaloids in American lupines, and pointed to the probability that most, if not all, the poisoning of live stock in America was due to these alkaloids and not to ictrogen.

(4) Extended field work has verified the conclusions of Sollmann and has shown that all aerial parts of the lupines examined are poisonous, the seeds being the most toxic, then in order the pods and leaves. This has been confirmed by preliminary experiments with extracts upon mice.

(5) The toxic substance is excreted by the kidneys; the intoxication is not cumulative, and animals may eat comparatively large quantities with no ill results, if the toxic limit is not reached at any one time. Inasmuch as the toxic and lethal limits are nearly the same, the prognosis for poisoned animals is not favorable.

(6) There is no form of remedial treatment that can be used advantageously for range animals. Poisoning in most cases can be avoided, even where the plant is abundant, by careful handling of the flocks, especial care being taken to see that hungry sheep are not grazed on fields where there is much lupine.

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